SYNTHESIS OF DERIVATIVES OF 2-AMINO-1,3,4-OXADIAZOLE-5-HYDROXAMIC ACID

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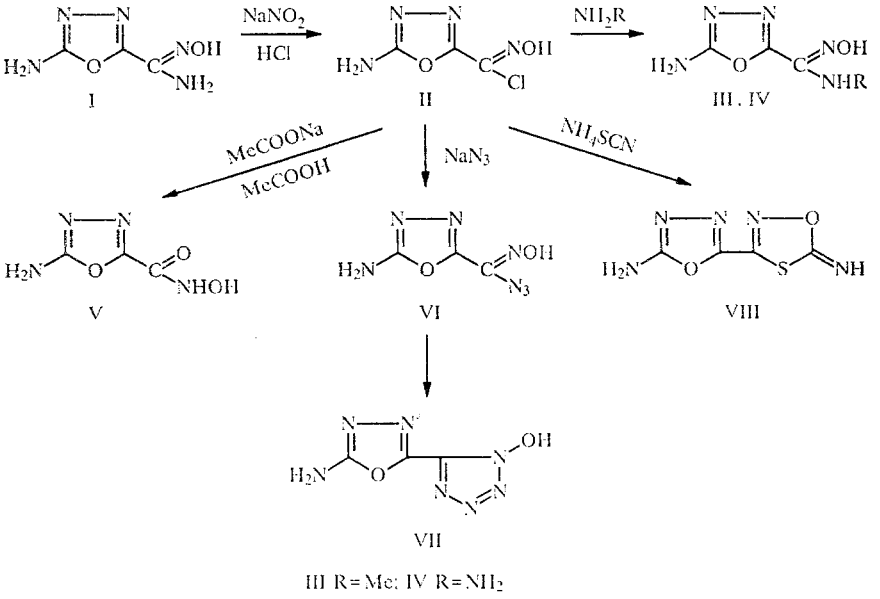
A series of derivatives of 2-amino-1,3,4-oxadiazole-5-hydroxamic acid has been prepared by the reaction of 2-amino-5-chloroximinomethyl-1,3,4-oxadiazole with nucleophiles.

Derivatives of 2-amino-1,3,4-oxadiazole are known to have a wide spectrum of biological activity [1, 2]. We have previously prepared 2-amino-1,3,4-oxadiazole-5-carboxamidoxime (I) and studied its conversion into 2-amino-5-(5R-1,2,4-oxadiazolyl-3)-1,3,4-oxadiazoles [3, 4].

In a continuation of the search for compounds with physiological activity, we have now synthesized derivatives of 2-amino-1,3,4-oxadiazole-5-hydroxamic acid. The traditional route to such compounds is the reaction of various nucleophiles with the acid chloride of the corresponding hydroxamic acid.



2-Amino-5-chloroximinomethyl-1,3,4-oxadiazole (II) was obtained in 78% yield by diazotization of the amidoxime (I). Reaction of the hydroximoyl chloride (II) with methylamine or hydrazine in methanol gave N-methyl-2-amino-1,3,4-oxadiazole-5-hydroxamide (III) and the hydrazide of 2-amino-1,3,4-oxadiazole-5-hydroxamic acid (IV) in yields of 52 and 42%, respectively.

On heating in aqueous acetic acid in the presence of sodium acetate the hydroximoyl chloride II hydrolyzed to 2-amino-1,3,4-oxadiazole-5-hydroxamic acid (V). The ^{1}H NMR spectrum of the acid V in DMSO-D_6 contained a singlet for the free amino group (7.5 ppm) and a broad signal (10.4 ppm) which evidently belonged to the NH and OH functions of the hydroxylamine unit [5]. The mass spectrum included a molecular ion peak at M^+ 144. Compound V also formed a characteristic red colored complex with $FeCl_3$ solution.

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Reaction of the hydroximoyl chloride II with aqueous sodium azide gave facile displacement of the chlorine atom by the azide group to give 2-amino-5-azidooximinomethyl-1,3,4-oxadiazole (VI) in 70% yield. The IR spectrum of compound VI contained an azide absorption band at 2180 cm^{-1}, while the ^1H NMR spectrum contained two singlets at 12.2 (OH) and 7.45 ppm (NH_2).

The conversion of 1,2,4-oxadiazole-3-carboxazidoxime into 3-(1-hydroxytetrazolyl-5)-1,2,4-oxadiazole under the influence of hydrogen chloride has been reported [6]. Cyclization of the azidoximinomethyl fragment into the hydroxytetrazolyl ring also occurred when gaseous HCl was passed through a dioxane solution of azide VI to give 2-amino-5-(1-hydroxytetrazolyl-5)-1,3,4-oxadiazole (VII) in 65% yield. The molecular ion peak at M^+ 169 was observed in the mass spectrum of compound VII. Absorptions characteristic of the azide group were absent from its IR spectra in the solid state and in DMF and chloroform solutions.

Hydroxamoyl chlorides are known to be converted into 1,4,2-oxathiazoles by the thiocyanate ion [7]. Reaction of the hydroximoyl chloride (II) with aqueous ammonium thiocyanate gave 3-(2-amino-1,3,4-oxadiazolyl-5)-5-imino-1,4,2-oxathiazole (VIII) in 91% yield. Thiocyanate absorption bands were absent from the IR spectrum of the cyclization product VIII and its ^1H NMR spectrum only contained signals for the amino (7.86 ppm) and imino (9.6 ppm) group protons. Elemental analysis results and the mass spectrum (M^+ 185) also confirmed the structure of compound VIII.

EXPERIMENTAL

Mass spectra were recorded with a Varian MAT CH-6 with an ionizing current of 60 eV and ionizing chamber temperature of 50-150°C. ^1H NMR spectra of $(CD_3)_2SO$ solutions were recorded with a Bruker WM-250 instrument and IR spectra of KBr disks were recorded over the 400-4000 cm^{-1} range with a Specord M-80 spectrometer.

Elemental analysis results for the compounds synthesized corresponded to the calculated values.

2-Amino-5-chloroximinomethyl-1,3,4-oxadiazole (II, $C_3H_3ClN_4O_2$). 10% HCl (20 ml) was added dropwise to a stirred suspension of 2-amino-1,3,4-oxadiazole-5-carboxamidoxime I (0.6 g, 4.2 mmoles) in water until solution was complete. Sodium nitrite (0.44 g, 6.3 mmoles) was then added in small portions at 0°C, stirring was continued for 30 min, the precipitate was filtered off and washed with water and acetone to give the product II (0.53 g, 78%), mp 236°C (dec.). M^+ 162, 164. ^1H NMR spectrum: 7.56 (2H, s, NH_2); 13.08 ppm (1H, s, NOH).

N-Methyl-2-amino-1,3,4-oxadiazole-5-hydroxamide (III, $C_4H_7N_5O_2$). Aqueous methylamine (1 ml) was added to a solution of the hydroximoyl chloride II (0.3 g, 1.8 mmoles) in methanol (20 ml). The solution was kept at room temperature for 30 min, then diluted with ether, the precipitate was filtered off and purified by TLC (silica gel, ethyl acetate) to give product III (0.145 g, 52%), mp 146°C (dec.). M^+ 157. ^1H NMR spectrum: 2.87 (3H, s, CH_3), 6.0 (1H, s, NH), 7.3 (2H, s, NH_2), 10.3 ppm (1H, s, NOH).

Hydrazide of 2-Amino-1,3,4-oxadiazole-5-hydroxamic Acid (IV, $C_3H_6N_6O_2$). The hydroximoyl chloride II (0.2 g, 1.2 mmoles) dissolved in methanol (15 ml) on heating. Hydrazine hydrate (1.8 mmoles) was added dropwise to the solution at room temperature and the reaction mixture was kept at this temperature for 1 h. The solvent was then removed in vacuum, the residue was diluted with ether, the precipitate was filtered off and purified as for compound III to give product IV (0.08 g, 42%), mp 265°C (dec.). ^1H NMR spectrum: 7.15 (2H, s, NH_2), 7.48 (2H, s, NH_2), 7.95 (1H, s, NH), 13.1 ppm (1H, s, NOH).

2-Amino-1,3,4-oxadiazole-5-hydroxamic Acid (V, $C_3H_4N_4O_3$). A mixture of the hydroximoyl chloride II (0.2 g, 1.2 mmoles) and sodium acetate (1 g, 12.1 mmoles) in 60% acetic acid (10 ml) was kept at 100°C for 2 h. It was then diluted with water, the precipitated crystals were filtered off, dissolved in 5% NaOH and reprecipitated with dilute HCl to give product V (0.138 g, 78%), mp 209°C (dec.). M^+ 144. ^1H NMR spectrum: 7.5 (2H, s, NH_2), 10.4 ppm (1H. br.s, NH, OH).

2-Amino-5-azidooximinomethyl-1,3,4-oxadiazole (VI, $C_3H_3N_7O_2$). Sodium azide (0.64 g, 9.8 mmoles) was added to a stirred suspension of the hydroximoyl chloride II (0.4 g, 2.5 mmoles) in water (20 ml). Stirring was continued for 3 h at room temperature, the precipitate was filtered off and washed with water and acetone to give product VI (0.29 g, 70%), mp 195°C (dec.). M^+ 169. ^1H NMR spectrum: 7.45 (2H, s, NH_2), 12.2 ppm (1H, s, NOH). IR spectrum: 2180, 2120 cm^{-1} (N_3).

2-Amino-5-(1-hydroxytetrazolyl-5)-1,3,4-oxadiazole (VII, $C_3H_3N_7O_2$). Compound VI (0.2 g, 1.2 mmoles) dissolved in dioxane (20 ml) on heating. Gaseous HCl was passed through the solution at room temperature until a precipitate began to form. The reaction mixture was kept at +5°C for 24 h, the precipitate was then filtered off and washed with water and acetone to give compound VII (0.13 g, 65%), mp 235°C (dec.). M^+ 169. ^1H NMR spectrum: 7.4 ppm (2H, s, NH_2).

3-(2-Amino-1,3,4-oxadiazolyl-5)-5-imino-1,4,2-oxathiazole (VIII, $C_4H_3N_5O_2S$). Ammonium thiocyanate (0.1 g, 1.3 mmoles) was added in portions to a stirred suspension of the hydroximoyl chloride II (0.2 g, 1.2 mmoles) in water (20 ml). Stirring was continued for 2 h and the precipitate was then filtered off and washed with water and acetone to give product VIII (0.2 g, 91%), mp 178°C (dec.). M^+ 185. ^1H NMR spectrum: 7.86 (2H, s, NH_2), 9.6 ppm (1H, br.s, NH).

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